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(54) Title: TOPICAL COMPOSITION CONTAINING AMINO ACID IN COMBINATION WITH EITHER INTERFERON OR THYMIDINE DERIVATIVES FOR TREATING VIRAL OR INFLAMMATION DISEASES

(57) Abstract

The invention relates to a medically beneficial preparation for outer use, containing amino acids which advantageously exerts augmenting effect on antiviral and inflammation inhibitory activities and is suitable to ameliorate or cure symptoms of psoriasis. The preparation is characterised by its containing one or more of the following amino acids: D- or L-aspartic acid, cysteine, cystine, glycine, oxyproline, serine, tyrosine, further it is containing - in a given case - interferon and/or antiherpetic thymidine-analogous drugs - preferably uridine derivatives and pharmaceutical additives, preferably solvents, conservatives or known ointment bases.

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TOPICAL COMPOSITION CONTAINING AMINO ACID IN COMBINATION WITH EITHER INTERFERON OR THYMIDINE DERIVATIVES FOR TREATING VIRAL OR INFLAMMATION DISEASES

Subject of the patent a medically beneficial preparation for outer use containing amino acids.

The preparation according to the patent description is advantageously applicable for augmentation of the antiviral and anti-inflammatory effects of interferons and thimidine-analogous antiherpetic drugs, for amelioration of psoriatic symptoms and further, it is an effective drug against Herpes virus infections.

Interferons are natural proteins with complex biological actions. Most important of their effects are antiviral, cell proliferation inhibitory and immune response enhancing properties.

These effects are utilised in the human therapy. Interferons have therapeutic use in tumour bearing patients.

Such applications are described in the following publications: J. biol. Regul. Homeostatic Agents, 1, pp 93-99 and 177-182, 1987; Intern. J. Cancer, 1987(Suppl.1.), pp 9-13, 1987; J. Interferon Res., Spec. Issue, 1992 Apr., pp 109-118.

Interferons are also effective in viral infections as it can be seen in the following publications: Lancet, i, p. 128, 1976; Transplantation Proc., 21, pp 2429-2430, 1989; Interferons in the Treatment of Chronic Virus Infections of the Liver, Pennine Press, Macclesfield, 1990.

They have also been proved beneficial in certrain inflammatory diseases: Neurology, 43, pp 655-661, 1993; J. Interferon and Cytokine Res., 15, pp 39-45, 1995.

The high doses applied for reaching a single therapeutic goal, however, may often provoke numerous non required side effects due to the complex actions of these proteins (J. Rheumatol., 20, pp 83-85, 1992; J.

Pediatr., 120(3), pp 429-431, 1992; Clin. Exp. Immunol., 90(3), pp 363-367, 1992).

These side effects are quite often dose-limiting factors in the therapeutic use of interferons.

It is usual to apply interferons in combination for therapeutic purposes in order to decrease the severity of side effects. Several different approximations are applicable for combination therapies: decrease of the necessary doses by complementation with drugs of similar mechanism of action (J. Natl. Cancer Inst., 83, pp 1408-1410, 1991); combination with drugs of antagonistic mechanism of action in order to selectively reduce harmful side effects (J. Biol. Resp. Modifiers, 5, pp 447-480, 19986); selective augmentation of the required therapeutic effect by addition of potentiating components or by application of appropriate physical conditions, e.g. hyperthermia (Proc. Soc. Exp. Biol. Med., 169, pp 413, 1982).

It is known from the publications that effective therapeutic application of thimidine-analogous drugs (deoxyuridine derivatives substituted at the 5 position) with antiherpetic action is seriously limited by that fact that a a fast viral resistance develops in response to therapeutic concentrations of these drugs. Viral strains resistant to one given drug show crossresistance to other ones with similar chemical structure. Dose reduction of these drugs -if it could be achieved- would reduce the selection pressure on the viruses, thus, the frequency of the developpent of resistant mutants consequently enhancing the therapeutic value of the known antiherpetic agents.

The purpose of this invention is to enhance selectively the antiviral effects of interferons and antiherpetic thimidine-analogues in order to be able to decrease the effective therapeutic doses.

It was also intended to develop a drug combination beneficial in herpetic infections and effective in reducing or eliminating skin symptoms of psoriasis.

The aim of the inventions is to produce such ointment and liquid for external use which contain low dose (and, thus, free of side effects) antiviral drugs (interfernon, 5-ethyl-2'-deoxyuridine=EDU, 5-ido-2'--deoxyuridine=IDU,) combined with components (amino acids) selectively potentiating the antiviral activity and the interferon-mediated inhibition of inflammation.

Our invention is based on the recognition that some amino acids are able to potentiate the antiherpetic effect of the thimidine analogue drugs by a factor of several grades (10^2 - 10^4 times) and likewise the antiviral and anti--inflammatory action of interferons without influencing other biological activities of interferons. Furthermore, the preparations are effective against Herpes viruses and alleviate or eliminate psoriatic symptoms of the skin.

Therefore, the core of the invention is a preparation for external use, containing amino acids, advantageously augmenting antiviral and anti-inflammatory drug actions and being benefical in psoriasis.

The preparation is characterised by its composition, containing one or more of the amino acids listed below -D- or L-aspartic acid (Asp), cysteine (Cys), cystine (cys), glycine (Gly), oxyproline (Opr), serine (Ser), tyrosine (Tyr)- and interferon or thimidine-analogous antiherpetic drugs -preferably uridine-derivaties- as required, furthermore, known pharmaceutical vehicles, preferably solvents, preservatives or known ointment bases.

The invention is introduced by the following examples.

Example 1

A sterile solution of native human interferon alpha (HuIFN-α) --preferably from the preparation under trade name EGIFERON- was made in water at a concentration of 50000 international units/ml (IU/ml) under aseptic conditions. The solution also contained an amino acid mixture of D-Asp and

L-Ser at a concentration of 5 mg/ml for each. 20 w/v% sucrose was added as a conserving agent.

Example 2

A sterile solution of native or recombinant human interferon gamma (HuIFN-γ) was made in water at a concentration of 2500 IU/ml and 15 mg/ml of D-Asp and L-Opr. 20 w/v% sucrose was added as a conserving agent.

Example 3

A sterile solution of IDU was made in water at a concentration of 25 µg/ml. 25 mg/ml of D-Asp was dissolved in the above solution. 20 w/v% sucrose was added as a conserving agent.

Example 4

A sterile solution of EDU was made in water at a concentration of 25 µg/ml. 1 mg/ml of L-Ser and 500 IU/ml of native or recombinant HuIFN-γ was added to the above solution. 20 w/v% sucrose was used as a conserving agent.

Example 5

Doses of HuIFN-α according to example 1. (at an IU/g ratio) were mixed with types and doses of amino acids described in the example 1. into a pharmaceutical ointment base (e.g. unguentum hydrophylicum) under aseptic conditions.

Example 6

The active ingredients described in the example 2. were mixed into a vehicle according to example 5. at a ratio shown in the exapmle 2. suitably substituting "g" for "ml".

Example 7

Antiviral activity of a HuIFN-α (in a prearranged concentration of 500 IU/ml) was measured on WISH (human amnion epithelia) cells against Vesicular stomatitis virus (VSV) in the presence of different amino acids under different experimental conditions. The antiviral test consists of 3 phases. In the I. phase WISH cells are incubated in 96-well flat-bottom microplates until reaching monolayer stage. 100 µl aliquots of twofold seral dilutions of the HuIFN-α samples are then added to the test cells and are incubated for 20-24 hours at 37 ^{o}C in 5% CO_2 atmosphere (phase II.). Finally the IFN-treated cells are infected with a predetermined dose of VSV which can kill 100% of the unprotected WISH cells in 24 hours (phase III.). The reference point of a measurement (the titre of HuIFN-α) is that dilution of the IFN sample which provides protection for 50% of the infected cells at the end of the 24 hours infection period. The effects of different amino acids and different conditions were compared by determining the virtual titres of HuIFN-α samples having identical nominal titres. The measurements were done:

a) in the presence of different amino acids at different concentrations in phase II. (Figure 1.)

b) in the presence of different amino acids at a concentration of 10 mg/ml in phase I., II. or III. (Figure 2.)

c) in the presence of differenct amino acid pairs in phase II. at individual concentrations of 5-5 mg/ml (Table I.)

1st amino acid	2nd amino acid						
	None	Asp	Cys	Gly	Opr	Ser	Tyr
None	100						
Asp	152	171					
Cys	95	109	82				
Gly	191	174	109	203			
Opr	107	167	102	223	132		
Ser	201	468	197	209	145	222	
Tyr	113	104	104	166	125	584	151

Table I.: Antiviral titres of the IFN-α samples treated with amino acid pairs in phase II. Results are given in % of the untreated control. The synergistic co-operation of Asp-Ser and Ser-Tyr pairs should be noted.

d) in the presence of different amino acid pairs in phase III. at individual concentrations of 5-5 mg/ml (Table II.)

1st amino acid	2nd amino acid						
	None	Asp	Cys	Gly	Opr	Ser	Tyr
None	100						
Asp	153	1722					
Cys	193	542	527				
Gly	134	161	192	143			
Opr	241	395	249	157	3424		
Ser	115	664	322	209	383	221	
Tyr	166	124	197	114	296	99	1568

Table II.: Antiviral titres of the IFN-α samples treated with amino acid pairs in phase III. Results are given in % of the untreated control. Most important pairings are: Asp-Ser, Asp-Cys, and the 10 mg/ml doses of Asp, Cys, Tyr and Opr (Asp-Asp, Cys-Cys, Tyr-Tyr and Opr-Opr pairs respectively). It also should be noted that phase III. is the most similar in conditions to the natural course of infections: the therapeutic drug is present simultaneously with the virus, not preceding it.

Example 8

The changes in the antiviral titres of HuIFN-γ samples upon amino acid (10 mg/ml) applications in phase II. or III. were examined in the system described in the example 7. (Table III.)

Amino acids	Effects in phase II.	Effects in phase III.
None	100	100
Asp	157	2263
Cys	53	1382
Gly	99	184
Opr	no antiviral activity	18101
Ser	481	598
Tyr	101	1695

Table III.: The effects of different amino acids applied in phase II. or III. on the antiviral titre of HuIFN-γ. Thy may observe the high potention in phase III. by Asp, Cys and Tyr, further, the extremely high (180-fold) augmentation by Opr.

Example 9

Antiviral activities of different concentrations of IDU were measured on a permanent human tumour cell line (Hep2) against human Herpes simplex type 1. Cells were incubated in Petri dishes until monolayer stage, then were infected with a predetermined dose of the challenge virus which can kill 100% of the unprotected cells in 72 hours. The virus was allowed for 1 hour to be adsorbed on the surface of the cells. Next, a fresh nutritive medium was given to the cells containing the drug in a concentration to be tested and the experimental system was incubated for 72 hours at 37 ^{o}C in 5% CO_2 atmosphere. The amount of virus produced in the test system was determined as follows: infected cells were disrupted, centrifuged and the supernatants were collected. Serial 10-fold dilutions were made from the supernatants and 100 µl aliquots were measured on Hep2 monolayers in 96-well flat-bottom microplates and incubated for 72 hours. $TCID_{50}$ values (dilutions which kill 50% of the test cells at the end of the incubation period) were determined for drug treated samples as well as for untreated controls. The antiviral effects of the drugs were calculated from the differences in virus production. Changes in the antiviral activity were measured in the presence of:

a) Ser in 5 mg/ml concentration (Figure 3.)

b) Asp in 5 mg/ml concentrtion (Figure 4.).

Example 10

Antiviral activities of different concentrations of EDU were determined in the simultaneous presence of 5 mg/ml Ser and of 250 IU/ml HuIFN-γ (Figure 5.) as described in the example 9.

Example 11

Herpes virus infections (HSV 1, Herpes zoster) and inflammatory skin rushes of different aetiology were treated with an ointment described in the example 5. Patients were chosen on voluntary basis and uncontrolled treatments were carried out. The results obtained are summarised in Table IV.

Disease	Number of cases	Treatment (daily applications/ number of days)	Results	Notice
labial herpes (HSV 1)	56 cases/27 persons	2-3/1-3	57/57 healings in 3 days	At 1 person vesicles extended to the neck and breast. Healing in 3 days. Ointment applied at the onset prevent the appearance of symptoms.
genital herpes (HSV 2)	1	2/7	Healing in a week	Widespread ulcerous infection on the leg.
zoster	5	2/5	5/5 healings in a week	Pain quits in 24 hrs. Crusting of vesicles starts in 72 hrs.
postzoster neuralgia	6	3/2-3	6/6 healings in 2-3 days	No known recurrences since 2 years.
decubitus	2	3/2	2/2 healings in 2 days	Livid skin, nonulcerous state. No symptoms developed again at the treated regions during further exposition (bed-bound state).
acne	17 cases/11 persons	2-3/2-5	15/17 healings	Recurrence frequency decreased at treated patients.
exanthema migrans	4 cases/3 persons	3/7	4/4 healings in 1 week	
traumatic haematoma	6	3/2	6/6 healings in 2-4 days	Reddening and disappearance instead of the usual coloration.
pruritus	1	2/2	Healing in 2 days	
inflammation due to irritation	1	3/1	2/2 healings in 24 hrs.	Diaper dermatitis due to adult incontinence.
inflammation of surgical wounds	1	3/2	Healing in 2 days	Sterile inflammation around the sutures.
purulent skin inflammation	2	2/1	2/2 healings in 1 day	Probably some anti-bacterial effects are also involved. In 1 case our treatment followed after 4 days ineffective tetracycline treatment.
inflammation of the outer ear cavity	1	3/1	healing in 1 day	Origin of inflammation unknown. No visible signs of infection. Treatment by earplugs.
"cold allergy"	3	3/1	3/3 healings in1 day	
skin rushes due to contact allergy	4	2-3/3	4/4 healings in 3 days	Allergens were bijoux necklaces, armbands or chromium watchbands.
psoriasis	7	2-3/2-10	5/7 healings	Not all types of disease are responsive.

What is claimed is:

1. Medically beneficial preparation for outer use, containing amino acids which advantageously exerts augmenting effect on antiviral and inflammation inhibitory activities characterised by that, it is containing one or more of the following amino acids: D- or L-aspartic acid, cysteine, cystine, glycine, oxyproline, serine, tyrosine, further it is containing - in a given case - interferon and/or antiherpetic thymidine-analogous drugs - preferably uridime derivatives and pharmaceutical additives, preferably solvents, conservatives or known ointment bases.

2. Medically beneficial preparation according to Claim 1 characterized by that, it is containing D-aspartic acid as amino acid.

3. Medically beneficial preparation according to Claim 1 characterized by that, it is containing D-aspartic acid and oxyproline as amino acids.

4. Medically beneficial preparation according to Claim 1 characterized by that, it is containing serine as amino acid.

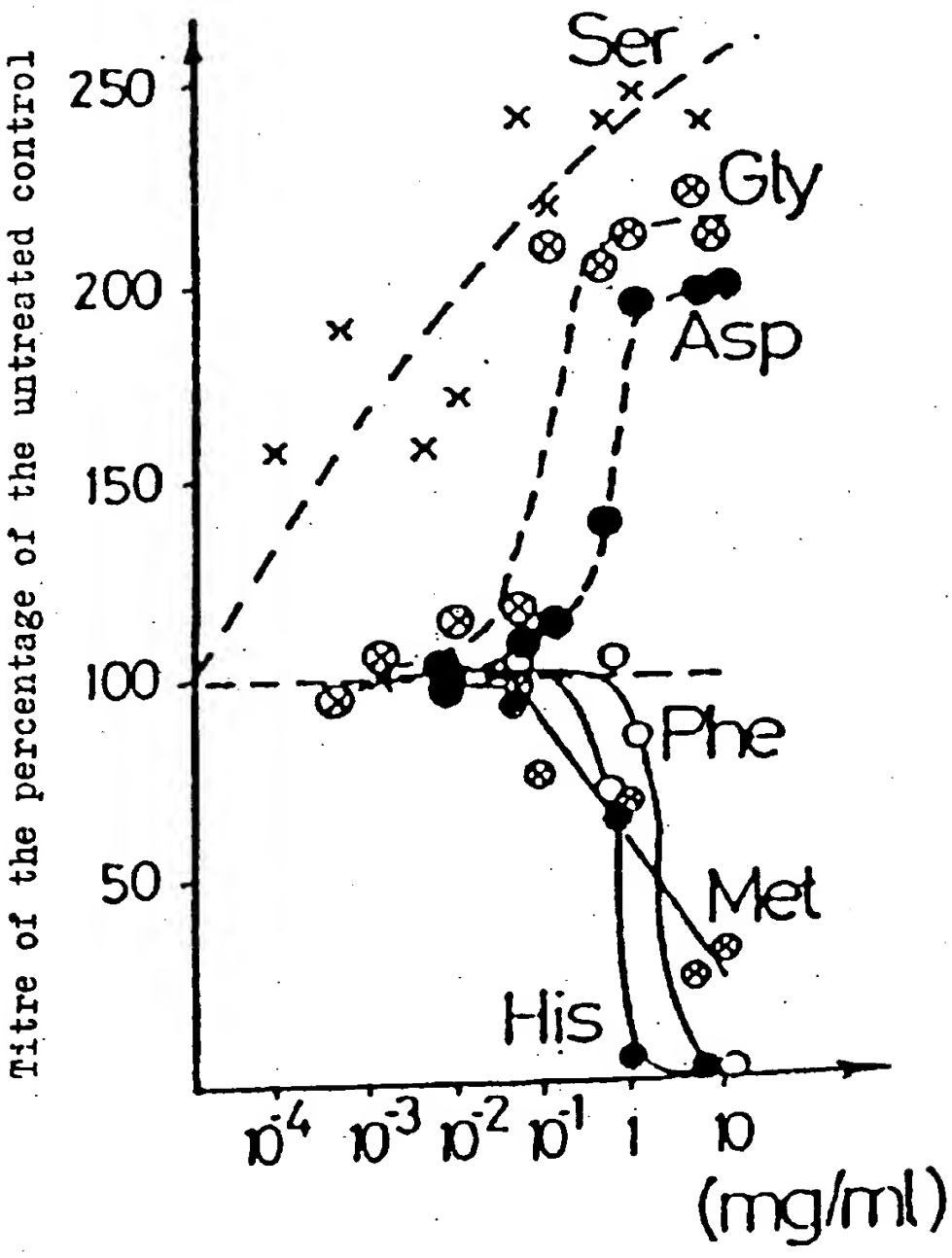
Titre of the percentage of the untreated control
250
200
150
100
50
Ser
Gly
Asp
Phe
Met
His
10^{-4} 10^{-3} 10^{-2} 10^{-1} 1 10
(mg/ml)
Amino acid concentration

FIG. 1

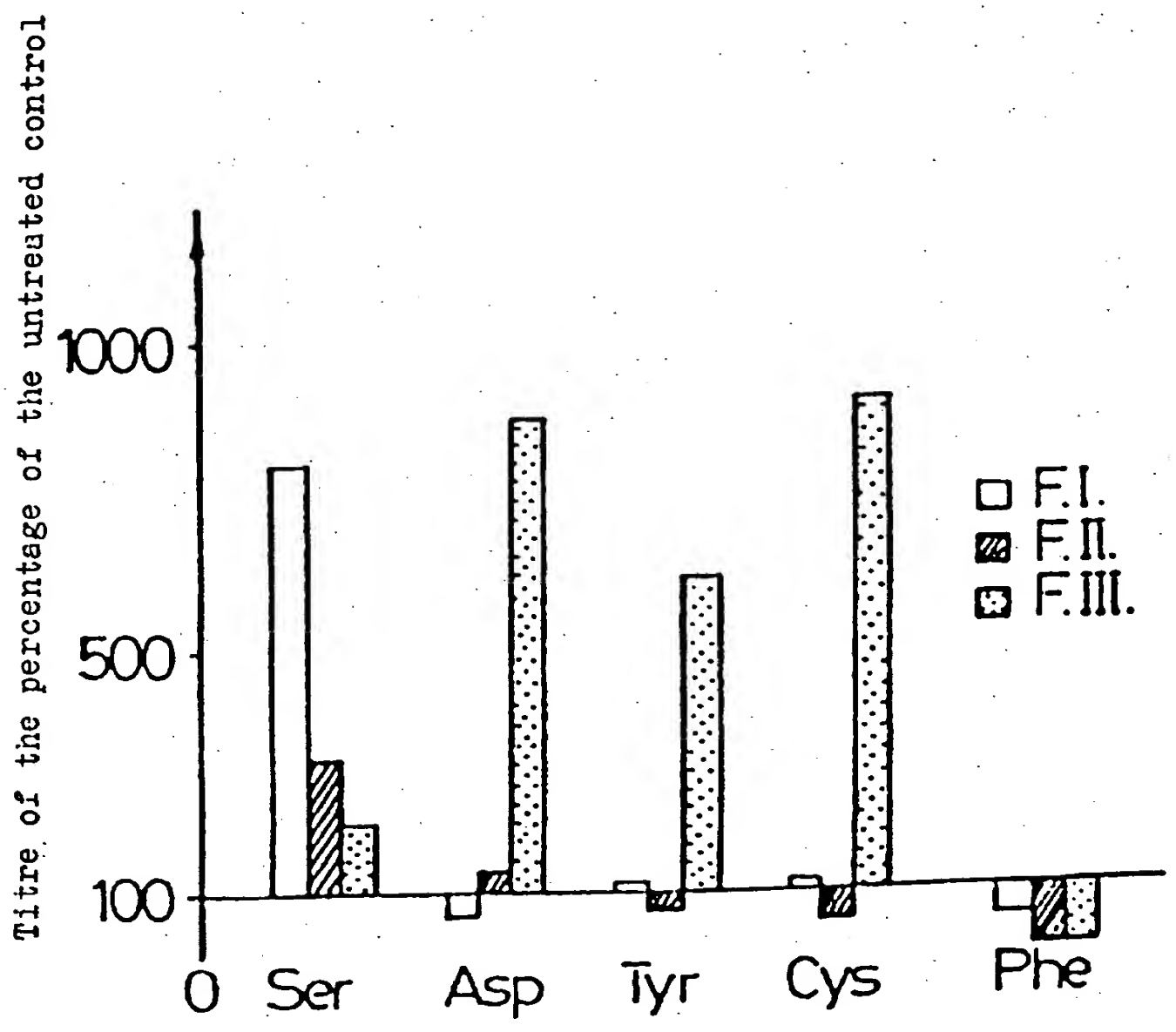
Titre of the percentage of the untreated control
1000
500
100
0
Ser
Asp
Tyr
Cys
Phe
F.I.
F.II.
F.III.

FIG. 2

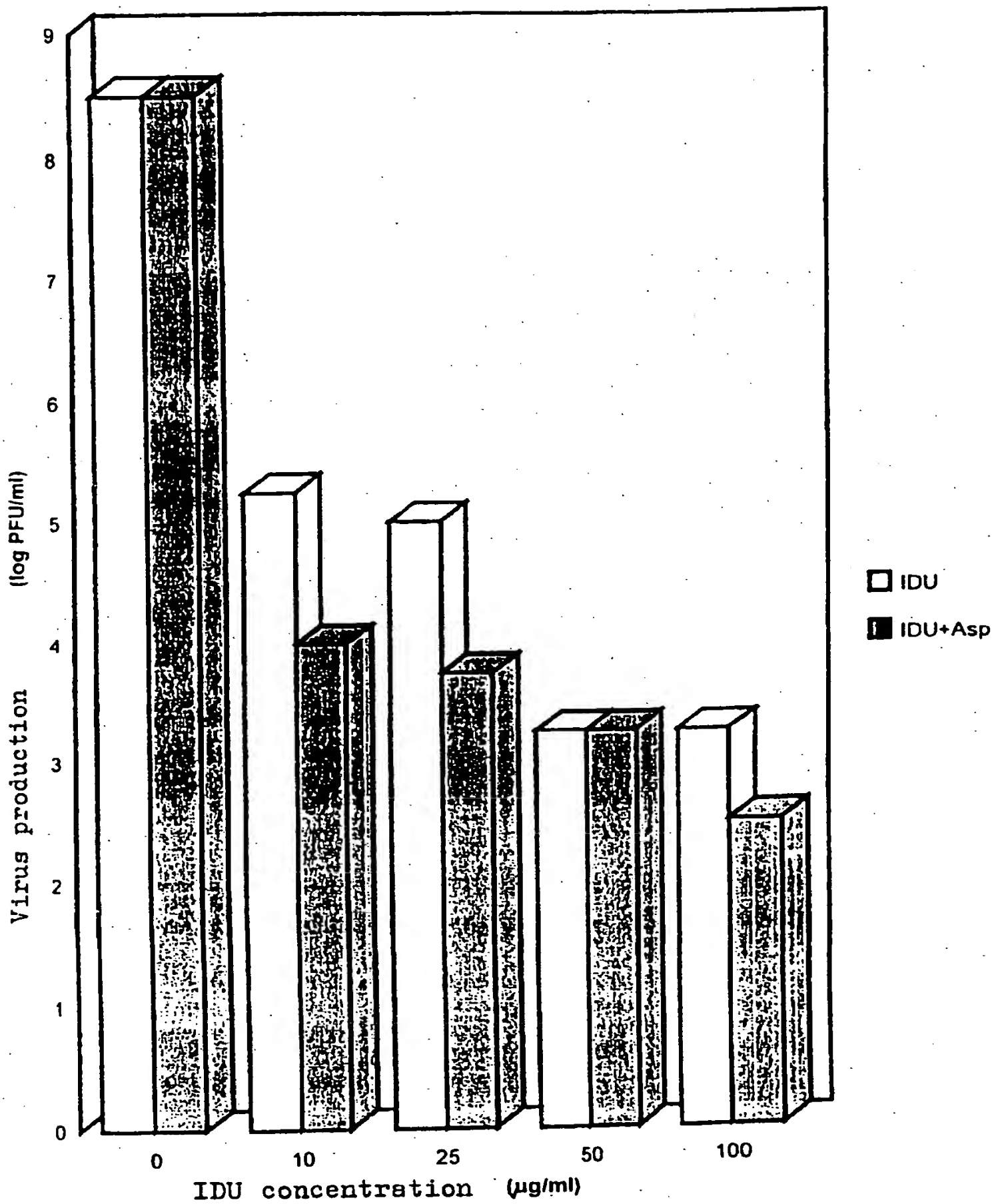
9
8
7
6
5
4
3
2
1
0
(log PFU/ml)
Virus production
0
10
25
50
100
IDU concentration (µg/ml)
IDU
IDU+Asp

FIG. 3

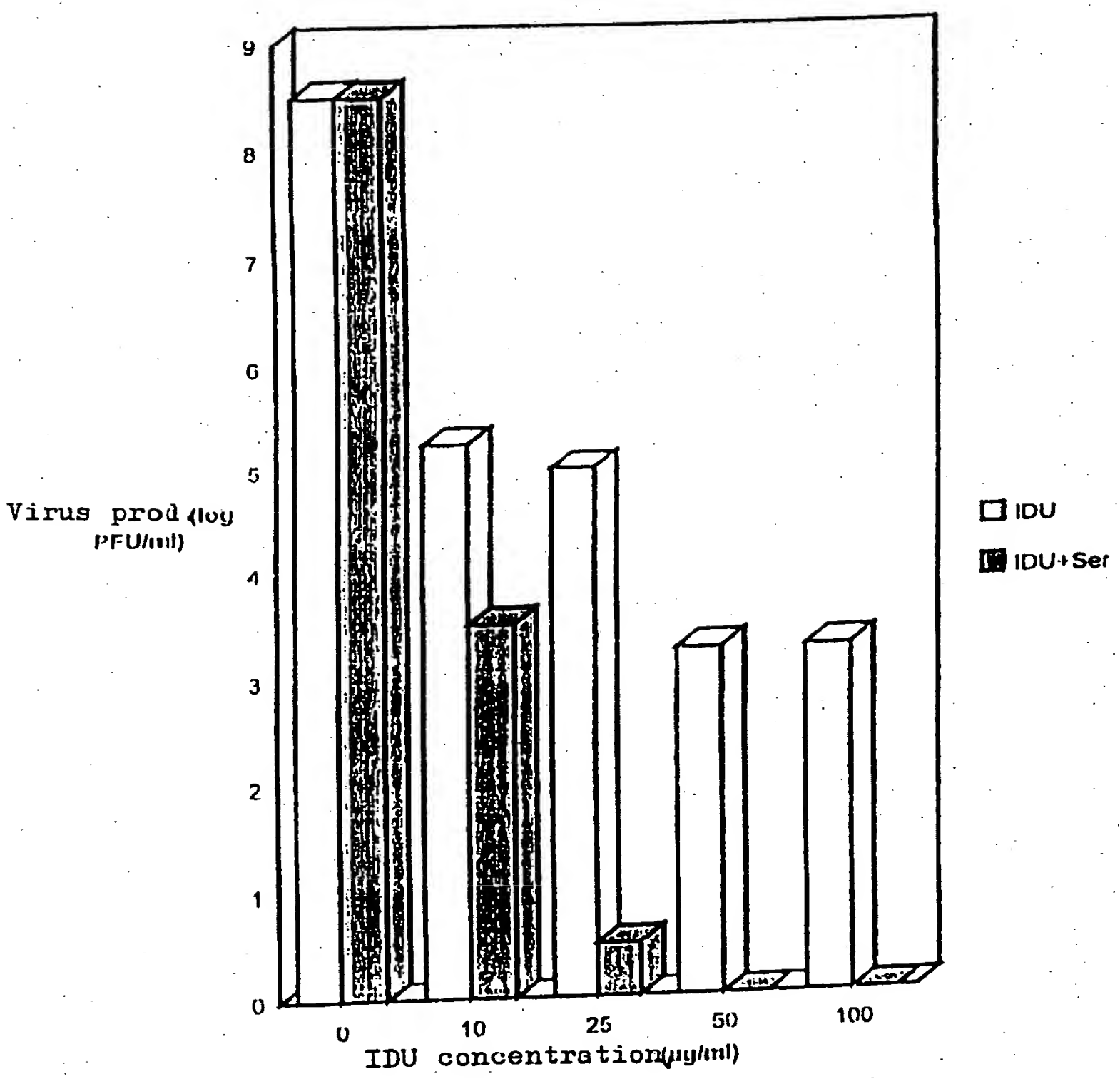
Virus prod (log PFU/ml)
9
8
7
6
5
4
3
2
1
0
0
10
25
50
100
IDU concentration(μg/ml)
IDU
IDU+Ser

FIG. 4

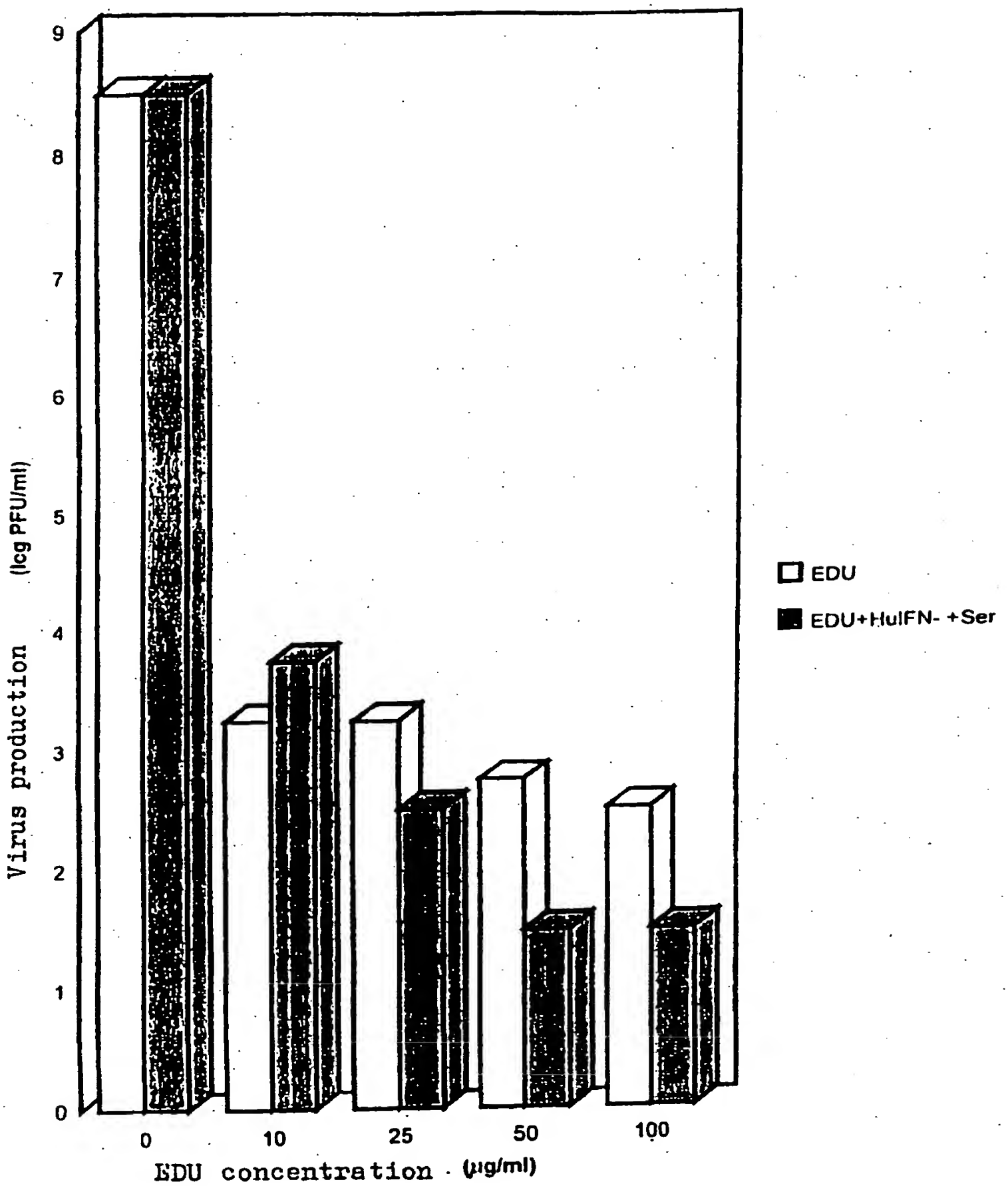
Virus production (lcg PFU/ml)
0
1
2
3
4
5
6
7
8
9
0
10
25
50
100
EDU concentration (µg/ml)
EDU
EDU+HulFN- +Ser

FIG. 5

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/21 A61K31/70 A61K31/195 //(A61K38/21,31:195), (A61K31/70,31:195)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	EP 0 326 151 A (SUMITOMO PHARMA ;KOKEN KK (JP)) 2 August 1989 * col.4, l.14; col.6, l.31; claims 12-14 * ---	1
X	US 4 710 376 A (EVANS SEAN A ET AL) 1 December 1987 * col.3, l.26; col.7, l.20; claims 1-4, 7 and 8 * --- -/--	1

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Date of the actual completion of the international search	Date of mailing of the international search report
21 January 1998	06.02.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Uiber, P

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